

## The contribution of Juan Rosai to the pathology of soft tissue tumors

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### Summary

The conceptual evolution in the field of soft tissue tumor pathology has been mostly driven by a relatively small group of individuals that includes giants of the past and the present such as James Ewing, Raffaele Lattes, Arthur Purdy Stout, Franz Enzinger, Sharon Weiss, Lennart Angervall, Harry Evans, Marku Miettinen, and Christopher Fletcher. Juan Rosai, not only exerted an immense impact on surgical pathology in general, but in consideration of his unique talent in identifying novel clinicopathologic entities, has also contributed remarkably to current understanding of mesenchymal neoplasms. The creation of desmoplastic small round cell tumor certainly ranks among his most relevant efforts, although he actually put his mark on a broad variety of soft tissue lesions, including vascular neoplasms. It would be impossible to include in a single article all the entities that he created or contributed to refine; therefore, this review is limited to a selection of what we believe represent true milestones.

**Key words:** Juan Rosai, soft tissue tumors, vascular tumors, mesenchymal tumors

### Introduction

The role of Juan Rosai in the foundation as well as the conceptual evolution of surgical pathology has been immense. His expertise spans all the main fields of pathology and mesenchymal tumors make no exception. In fact, current classification of soft tissue tumors<sup>1-3</sup> is strongly influenced by his many contributions. In addition to describing several new entities, he greatly improved our understanding of mesenchymal neoplasms, particularly in the field of vascular tumors. In consideration of the vast influence exerted by Dr. Rosai, this review will focus on a selection of clinicopathologically relevant tumor entities.

### Desmoplastic Small Round Cell Tumor

Desmoplastic small round cell tumor (DSRCT) certainly represents one of Rosai's major contributions to the field of mesenchymal oncologic pathology. A series of 19 cases collected within the files of Juan Rosai, describing a highly malignant polyphenotypic mesenchymal neoplasm affecting young individuals, was first presented at the annual meeting of the US and Canadian Academy of Pathology (USCAP), held in Chicago in March 1991. The series was subsequently published in *The American Journal of Surgical Pathology*<sup>4</sup>. Based on morphology, represented by a predominantly round cell proliferation set in densely fibrous stroma, Gerald and Rosai named this new entity as DSRCT. The very first description actually

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#### Conflict of interest

The Authors declare no conflict of interest.

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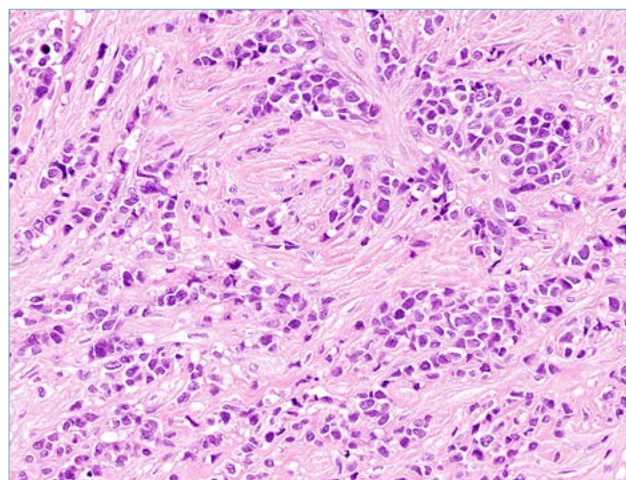
dates to 1988 when a case report was presented at USCAP and subsequently published in the *Journal of Pediatric Pathology* <sup>5</sup>.

Desmoplastic small round cell tumor is characterized by a very distinct clinicopathologic presentation. The vast majority of patients are children and young adults (age ranging from first to fifth decades of life) with a strong male predominance (4:1). Desmoplastic small round cell tumor primarily arises in mesothelium-lined anatomic regions, the abdominal cavity being the most common location. Documented localizations outside the abdominal cavity are rare and include the pleura <sup>6</sup> and the tunica vaginalis <sup>7</sup>. Exceptional extra-serous locations are represented by kidney <sup>8</sup>, head and neck <sup>9</sup>, posterior cranial fossa <sup>10</sup> and limbs. Clinical presentation is related to the primary site of involvement. If intra-abdominal, symptoms may become evident only in presence of masses of large size. In this context, pain, palpable mass, abdominal distention and/or obstruction are common complaints. Multiple early serosal implants are common and synchronous metastases to locoregional lymph nodes and liver have been observed. The typical gross appearance of DRCT is that of a firm gray-white tumor with multiple smaller satellite nodules. Foci of necrosis and hemorrhage are often present.

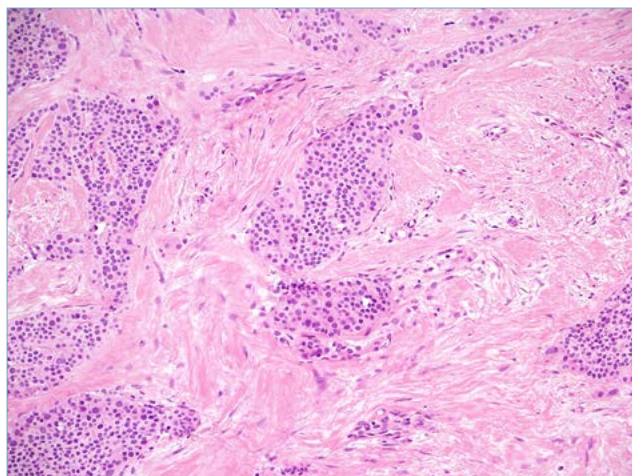
Histologically, the more classic form is composed of sharply demarcated nests or cords of small round cells set in a prominent collagenous desmoplastic stroma (Fig. 1A). In typical cases, the neoplastic cells are uniform with a small to medium sized hyperchromatic nucleus, and inconspicuous nucleoli. The amount of cytoplasm is variable (from scant to abundant). More rarely, the cellular elements may present

as, epithelioid (Fig. 1B), signet-ring like or spindled. A minority of cases show rhabdoid morphology with intracytoplasmic eosinophilic inclusions. Significant nuclear pleomorphism is exceedingly rare. In approximately one-third of cases growth patterns vary from tubular to insular. Mitoses, central cystic degeneration and areas of necrosis are very frequent. It may happen that the desmoplasia is limited to the extent that it can be easily overlooked (Fig. 1C).

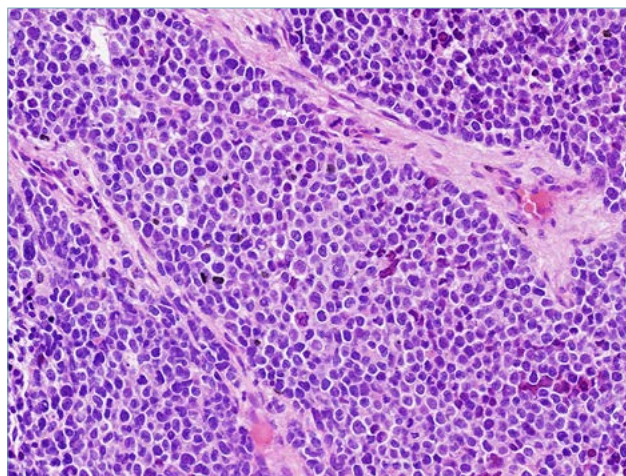
The polyphenotypic immunohistochemical expression of DSRCT represents a major clue to diagnosis <sup>11</sup>. Neoplastic cells express epithelial (pancytokeratins



**Figure 1B.** Desmoplastic small round cell tumor. Rarely neoplastic cells features an epithelioid morphology mimicking metastatic carcinoma



**Figure 1A.** Desmoplastic small round cell tumor. Most often the tumor is composed of clusters of round cells set in densely fibrous stroma.

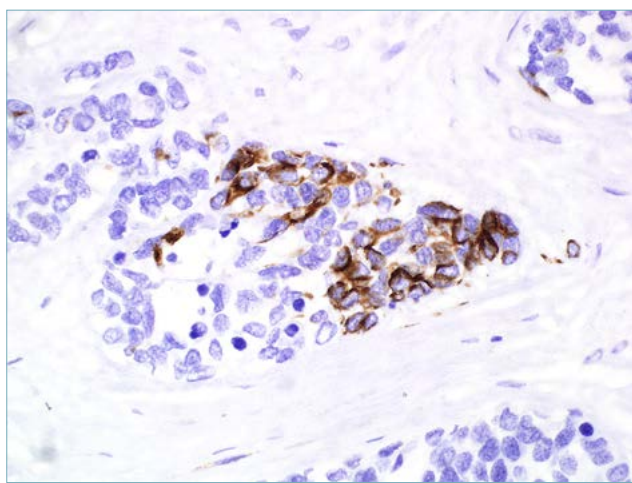


**Figure 1C.** Desmoplastic small round cell tumor. Exceptionally, desmoplastic stroma can be absent.

and EMA), muscular (desmin at times featuring a dot like cytoplasmic signal) (Fig. 1D), and neural markers (NSE, S100 and CD57). EMA is the more sensitive marker to demonstrate epithelial differentiation in DSRCT. The expression of neural markers is highly variable. CD99 shows diffuse cytoplasmic positivity in less than 20% of cases lacking a crisp membrane staining as typically seen in Ewing's sarcoma. Due to the *WT1/EWSR1* gene fusion (discussed later) nuclear c-terminus WT1 antibodies may identify the truncated protein product in the vast majority of cases<sup>11</sup>. Markers of striated muscle differentiation such as myogenin are consistently negative.

Cytogenetically, DSRCT is characterized by a recurrent t(11;22)(p13;q12) translocation leading to a *EWSR1/WT1* gene fusion<sup>12</sup>. The *EWSR1/WT1* fusion transcript has transcriptional regulatory activity and is a highly specific and sensitive molecular marker detectable in up to 97% of DSRCT cases<sup>13</sup>. Very recently the same molecular alteration has been reported in tumors showing morphological and immunophenotypic features unrelated to DSRCT<sup>14</sup>. These entities have not been well characterized yet, and represent a potential diagnostic pitfall if molecular genetics is not evaluated in context with morphology.

The differential diagnosis includes other round cell sarcomas (Ewing sarcoma and alveolar rhabdomyosarcoma), malignant mesothelioma and metastatic carcinoma. The combination of CD99 and NKX2.2 positivity favor the diagnosis of Ewing sarcoma<sup>15</sup>. By contrast the identification of *EWSR1* gene rearrangement is not sufficient to support a diagnosis of Ewing's sarcoma. It is, in fact, necessary to demonstrate the presence of Ewing's sarcoma-specific fusions (most



**Figure 1D.** Desmoplastic small round cell tumor. Immunopositivity for desmin is almost always observed.

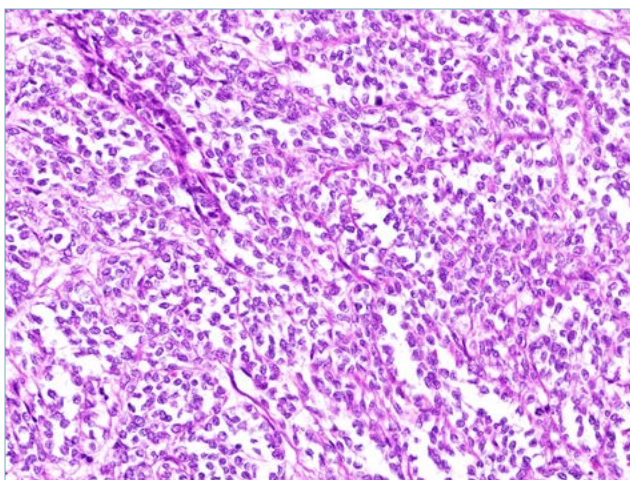
often *EWSR1-FLI1* followed by *EWSR1-ERG*). The solid variant of alveolar rhabdomyosarcoma in addition to the expression of desmin features positive immunohistochemical staining for myogenin that is never observed in DSRCT. Malignant mesothelioma usually affects older individuals, most often lacks a desmoplastic stroma, shows positivity for mesothelial markers such as calretinin, and often exhibits loss of nuclear expression of BAP1. Metastatic neuroendocrine carcinoma also generally affects older patients, although considering significant potential immunophenotypic overlap absence of *EWSR1-WT1* gene fusion may help in ruling out DSRCT.

Improved survival is obtained through high-dose chemotherapy and extensive debulking surgery. Nonetheless, despite multimodal treatment, with a 15% 5-year overall survival rate DSRCT remains an aggressive malignancy<sup>16</sup>.

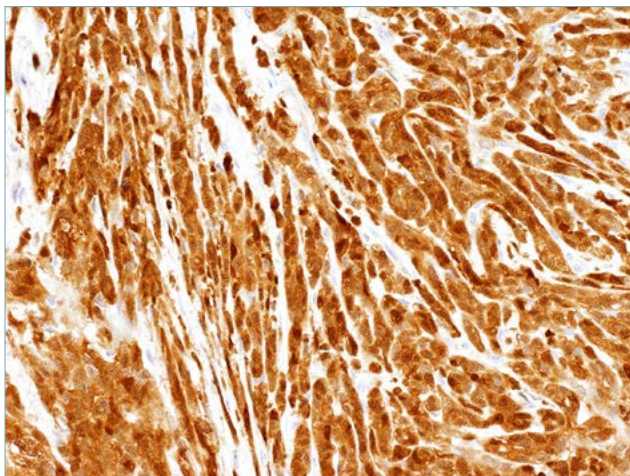
### Malignant Gastrointestinal Neuroectodermal Tumor

Malignant gastrointestinal neuroectodermal tumor (GNET) is the label first proposed by Stockman et al in 2012 to describe a mesenchymal malignancy closely related to clear cell sarcoma (CCS) of soft tissue but most often lacking overt melanocytic differentiation<sup>17</sup>. Actually, the very first description of this entity dates to 2002, when Rosai reported it under the descriptive term “osteoclast-rich tumor of the gastrointestinal tract with features resembling clear cell sarcoma of soft parts”<sup>18</sup>. Malignant gastrointestinal neuroectodermal tumor and clear cell sarcoma of soft tissue are extremely rare and are classified by WHO classification of soft tissue in the group of tumors of uncertain differentiation<sup>1</sup>. Clear cell sarcoma was first reported in 1965 by Enzinger, as a tumor arising in the deep soft tissues of the distal extremities<sup>19</sup>. Subsequently Enzinger himself coined the alternative label “melanoma of soft parts”<sup>20</sup>, although despite some morphologic similarities, CCS is clinically, pathologically and genetically distinct from cutaneous melanoma. Clear cell sarcoma occurs predominantly in adolescents and young adults, with a peak incidence between 20 and 40 years of age. In addition to the limbs, CCS has also been reported in the head/neck region including the oral cavity, in the trunk, and in the viscera including the lung and gastrointestinal tract<sup>21-26</sup>. Interestingly, CCS of the GI-tract (M-GNET), exhibits morphologic and immunophenotypic features distinct from those arising in the somatic soft tissue. Histologically, both CCS and M-GNET are composed of macronucleolated epithelioid and spindle cells, organized in large nodules

demarcated by thick fibrous septa. Despite the name, the clear cell component is actually scant with the majority of cells showing eosinophilic cytoplasm. As first reported by Rosai, multinucleated giant cells are seen in half of cases. In M-GNET the most distinctive morphologic feature is represented by the presence of pseudopapillary and/or pseudoalveolar patterns of growth (Figs. 2A, 2B). Genetically CCS and M-GNET share a translocation  $t(12;22)(q13;q12)$ , fusing *EWS* and *ATF1* genes<sup>27</sup>. A translocation  $t(2;22)(q34;q12)$ , resulting in an *EWSR1-CREB1* gene fusion seems to cluster in M-GNET<sup>24,27</sup>.



**Figure 2A.** Malignant gastrointestinal neuroectodermal tumor. One of the distinctive features is the presence of pseudopapillary pattern of growth.



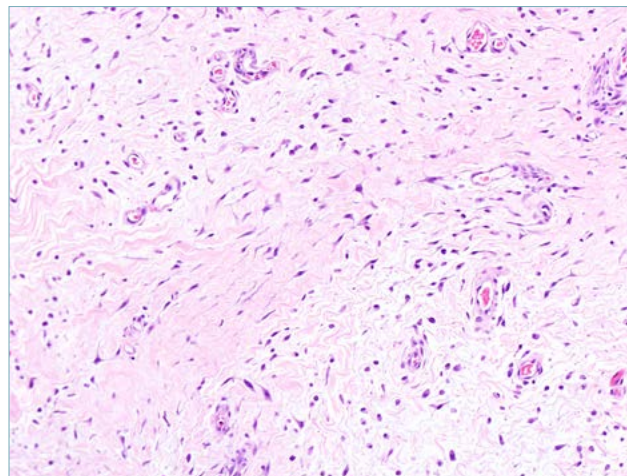
**Figure 2B.** M-GNET is diffusely S100 positive.

## Deep “Aggressive” Angiomyxoma

In 1983, Steeper and Rosai published a series of 9 female patients affected by distinctive myxoid soft tissue tumors of the pelvic and perineal region<sup>28</sup>. Aggressive angiomyxoma was the label used to describe it, to emphasize its locally infiltrative, and recurrent nature. Deep angiomyxoma (DA) is an alternative term to suggest that its aggressiveness was probably somewhat overestimated. Deep angiomyxoma represents the label of choice in current soft tissue WHO classification<sup>1</sup>, with the term “aggressive” left in brackets mainly for historical reasons.

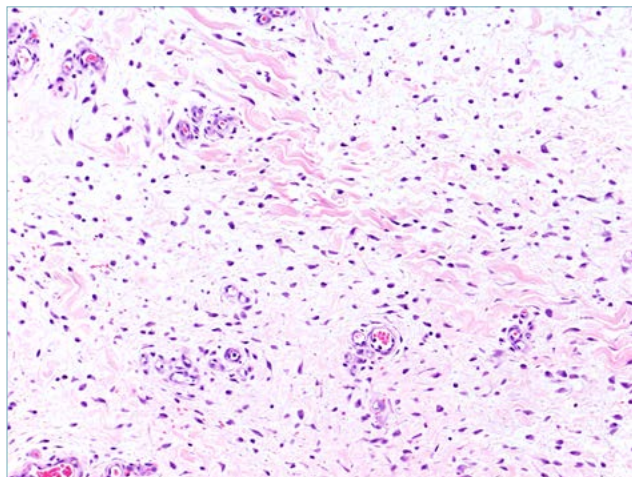
Deep angiomyxoma typically occurs in the deep soft tissues of the perineal region of young to middle-aged (age range from 14 to 77 years old) women. A striking female predominance (5:1) is observed however the same entity can exceptionally be observed in male patients. Vulva, perineum, deep pelvic soft tissues, inguinal area, gluteal region and retroperitoneum have all been described as common locations for this unusual tumor<sup>29</sup>. Deep angiomyxoma presents as a slow-growing, deep-seated and often painless mass, which may be clinically silent for years. Only when DA attains a large size is it associated with local pain. On gross examination, deep angiomyxoma is most often represented by a large soft mass (most measure > 10 cm) with ill-defined margins.

The microscopic appearance of DA is that of an ill-defined infiltrative lesion composed of spindle or stellate stromal cells scattered among copious amounts of loose edematous myxoid stroma (Fig. 3A). A prominent vascular network is invariably present. The lesions are



**Figure 3A.** Deep angiomyxoma. The lesion is ill-defined and composed of spindle or stellate stromal cells set in a myxoid stroma.

typically hypocellular. Lesional spindle cells exhibit low mitotic activity and are cytologically bland with oval to rounded nuclei and fine bipolar eosinophilic cytoplasmic processes (Fig. 3B). Clusters of smooth muscle cells (so-called myoid bundles) are frequently seen.



**Figure 3B.** Deep angiomyxoma. Nuclear atypia is minimal.

The neoplastic spindle cells stain positively, either diffusely or more rarely focally, for desmin and smooth muscle actin<sup>28</sup>. CD34, ER and PR are also commonly positive in stromal cells.

Genetically, recurrent balanced *HMGA2* (12q14.3) gene rearrangements represent a distinctive molecular aberration in approximately one-third of cases<sup>30</sup>. The expression of HMGA2 protein expression represent a sensitive but not entirely specific diagnostic marker<sup>31</sup>.

The differential diagnoses include myxoma, atypical lipomatous tumor, myxoid liposarcoma, low grade myxofibrosarcoma, myxoid neurofibroma, angiomyofibroblastoma, and other soft tissue tumors with secondary myxoid changes.

Due to highly infiltrative pattern of growth disease-free margins are often difficult to achieve. Hence, local recurrences are not uncommon (from 9% to 50%) even decades after initial excision. It is common experience however that local recurrences have a tendency to be self-limiting.

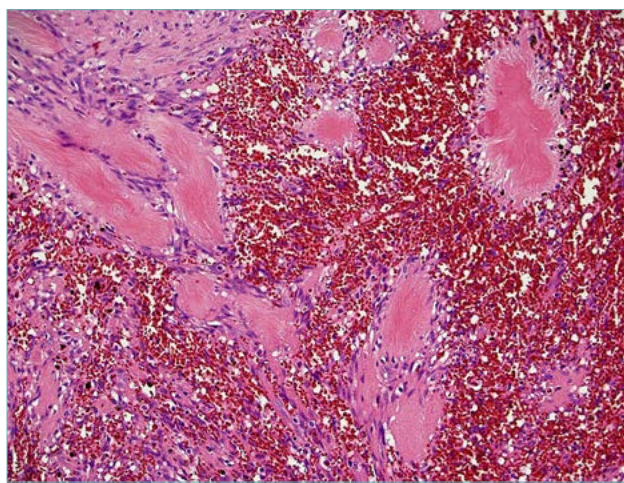
### Intranodal Palisaded Myofibroblastoma

In May 1989, Suster and Rosai described a rare benign mesenchymal tumor occurring within lymph

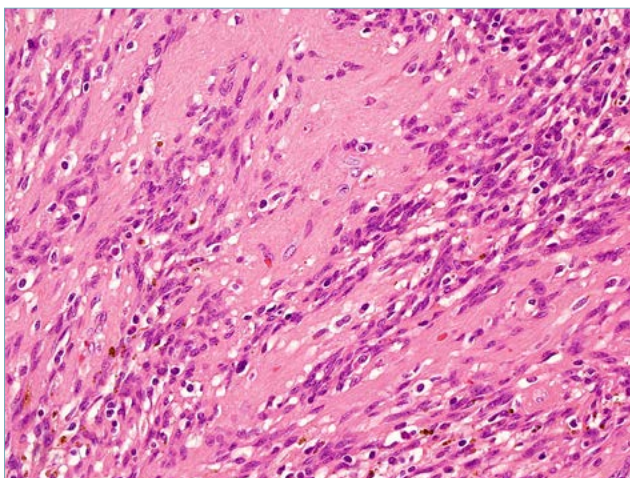
nodes using the descriptive term “intranodal hemorrhagic spindle-cell tumor with “amiantoid” fibers”<sup>32</sup>. At the same time, Weiss reported an identical lesion using the alternative term “palisaded myofibroblastoma”<sup>33</sup> whereas Lee utilized the descriptive term “solitary spindle cell tumor with myoid differentiation of the lymph-node”<sup>34</sup>. In 1992, Fletcher introduced the term “intranodal myofibroblastoma” (IM) to emphasize the predominant intranodal occurrence<sup>35</sup>. Intranodal myofibroblastoma generally affects middle aged adults with a peak incidence in the fifth decade, however age range at presentation is rather broad (19 to 78 years). A slight male predominance (2:1) is observed. Most cases seem to predilect inguinal lymph nodes<sup>32</sup>, although occurrence in axillary, submandibular, and mediastinal lymph nodes has also been reported<sup>35</sup>. They appear clinically as single slow-growing painless masses which vary in size from 1 to 4 cm.

Grossly, most cases are well circumscribed, featuring a gray-white cut surface with hemorrhagic areas. Exceptional cases show multifocality.

Microscopically, IPM appears as a well circumscribed spindle cell lesion centered in lymph nodes. The neoplastic myofibroblasts are arranged in a fascicular pattern, set in an abundant collagenous matrix, around which they often assume a palisading arrangement. The extracellular collagen organizes in stellate-shaped structures resembling (but not representing) amiantoid fibers (Fig. 4A). “Amiantoid fibers” are present throughout the lesion in virtually all cases, showing a paler center (collagen type I) often containing a central vessel and a more eosinophilic and darker rim (collagen type III) with stellate periphery. The myofibroblastic component is cytologically bland



**Figure 4A.** Intranodal myofibroblastoma. So-called “amiantoid fibers” represent a major clue to diagnosis.



**Figure 4B.** Intranodal myofibroblastoma. The tumor is composed of cytological bland spindle cells.

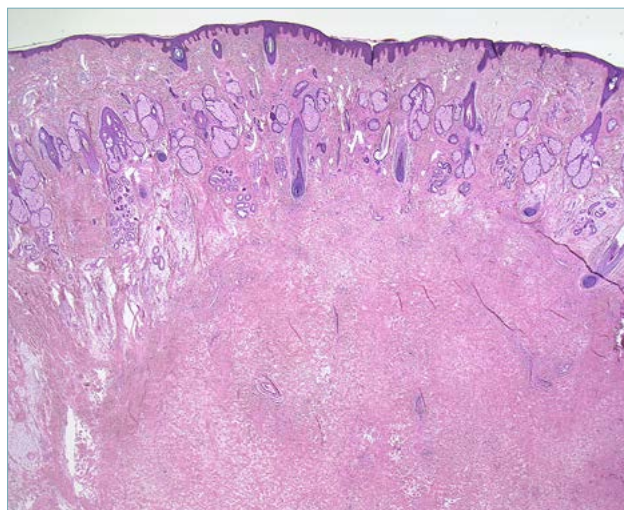
featuring oval nuclei and pale eosinophilic cytoplasm (Fig. 4B). Another peculiar finding is the presence of paranuclear eosinophilic globules that is observed in approximately half of cases.

Neoplastic cells are consistently positive for smooth muscle actin, and occasionally for desmin, but negative for CD34 and S100. Hotspot *CTNNB1* missense mutations can be detected in the vast majority of IPMs, leading to nuclear accumulation expression of  $\beta$ -catenin<sup>36</sup>. The differential diagnosis of IPM includes metastatic lesions (most often malignant melanoma), benign schwannomas, follicular dendritic cell sarcomas, and intranodal Kaposi sarcomas. Schwannomas are consistently and diffusely S100 positive, and characterized by the presence of hyalinized blood vessels and in classic examples by the alternation of Antoni-A and Antoni-B areas. Follicular dendritic cell sarcomas are consistently CD21, CD23 and clusterin positive and typically feature the presence of lymphocytes scattered throughout the lesion. Intranodal KS is characterized immunohistochemically by expression of endothelial markers and, most importantly HHV8.

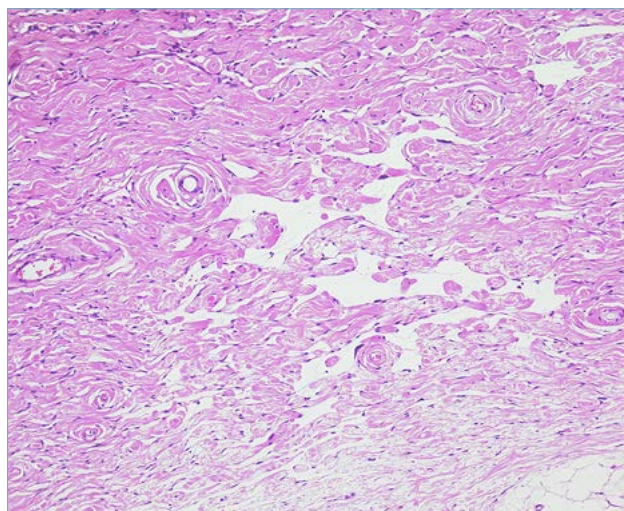
Intranodal myofibroblastoma is a benign lesion with no evidence of malignant transformation or metastatic spread. Surgical excision is curative with rare local recurrences observed in approximately 6% of cases.

### Ectopic Meningothelial Hamartoma

Ectopic meningothelial hamartoma (EMH) has been reported as a benign soft tissue lesion of the scalp, by Suster and Rosai in 1990<sup>37</sup>. Meningothelial hamarto-



**Figure 5A.** Ectopic meningothelial hamartoma. At low power branching empty spaces ramified in the dermis and subcutis are appreciated.



**Figure 5B.** Ectopic meningothelial hamartoma. The ectatic pseudovascular spaces, embedded in abundant collagen stroma, are lined by epithelioid neoplastic cells.

ma is most often an incidental clinical finding and is described clinically as a slow-growing subcutaneous mass that principally affects the head and neck region. The skin of the scalp is the most common anatomic site. Meningothelial hamartoma is extremely rare, and display a slight female predominance. Age at presentation shows bimodal peaks in the second and between the fifth to sixth decades of life. Congenital and perinatal lesions have been reported.

Microscopically EMH is composed of ectatic pseudo-vascular spaces lined by epithelioid cells that exhibit an infiltrative, ramified pattern of growth (Figs. 5A, 5B). Multinucleated giant cells and well-formed psammoma bodies may be occasionally observed.

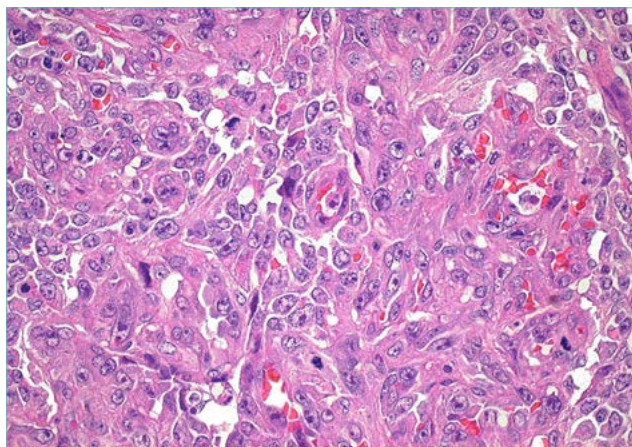
The immunohistochemical profile of the meningeothelial cellular element is comparable to that of meningeothelial cell. Lesions show positivity for EMA and variable expression of progesterone receptors. In consideration of its “infiltrative” pattern of growth, EMH may mimic angiosarcoma. Negativity for endothelial markers and absence of cytologic atypia represent important clues in the differential diagnosis.

Surgical resection with clear margins is curative, and only a few cases have reported local recurrences.

## Vascular neoplasms

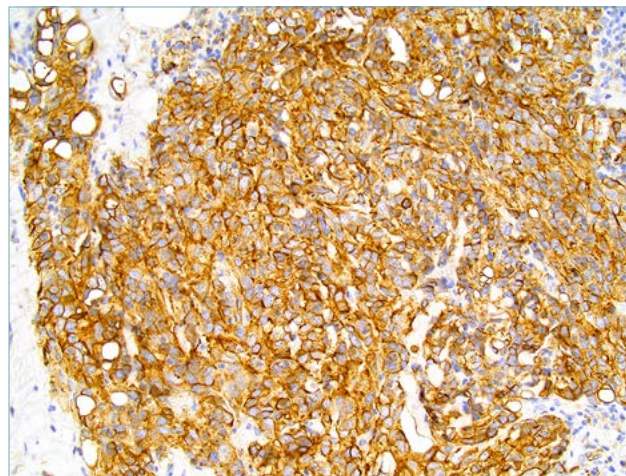
### EPITHELIOID ANGIOSARCOMA

Juan Rosai's contributions to the field of vascular neoplasms is really remarkable. In fact, we owe to him the first description of epithelioid angiosarcoma, first in the skin<sup>38</sup>, and subsequently in the thyroid<sup>39</sup>. In the context of cutaneous vascular malignancies, he specifically mentioned the possibility that angiosarcoma could present as a predominantly solid, non-vasoformative lesion, mimicking undifferentiated carcinoma (Fig. 6A). Inspired by Rosai's observations, epithelioid angiosarcoma of deep soft tissues was then first introduced by Fletcher et al in 1991<sup>40</sup>. Epithelioid angiosarcoma oc-



**Figure 6A.** Epithelioid angiosarcoma. The tumor is composed of atypical epithelioid neoplastic cells showing prominent nucleoli and organized in solid nests with non-vasoformative features. In this situation the main differential diagnosis includes either metastatic carcinoma or metastatic melanoma.

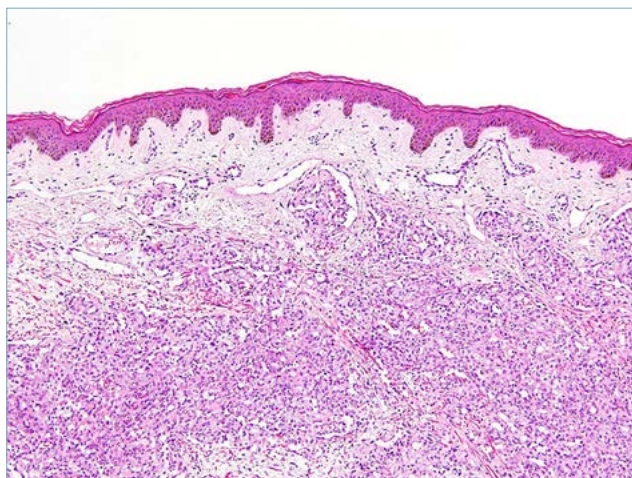
curs most often in the deep soft tissue and at visceral locations of adult patients. Whenever clear vasoformative features are missing the differential diagnosis is broad and include proximal-type epithelioid sarcoma (ES), epithelioid malignant schwannoma, metastatic amelanotic melanoma and metastatic carcinoma. Immunohistochemistry plays a key diagnostic role. Proximal type ES most often features a rhabdoid morphology, is cytokeratin diffusely positive and consistently exhibits loss of nuclear expression SMARCB1 (INI1). The latter is also observed in approximately 70% of epithelioid malignant schwannoma in association with diffuse S100 immunopositivity. Angiosarcoma consistently express CD31 (Fig. 6B) and ERG. In this context, both ERG and CD34 are not that helpful as they are also expressed in approximately half of epithelioid sarcomas. Importantly, expression of cytokeratin is shared by epithelioid sarcoma, carcinoma and angiosarcoma further proving that the use of single immunohistochemical markers represents a potential source of diagnostic inaccuracy.



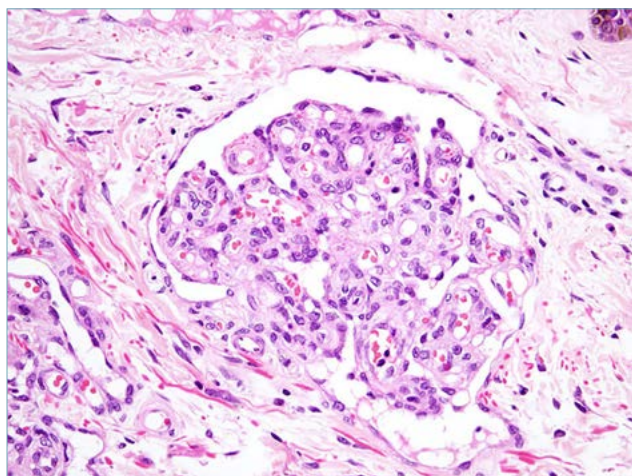
**Figure 6B.** Epithelioid angiosarcoma. Immunostaining for CD31 is almost always observed.

### GLOMERULOID HEMANGIOMA

The term glomeruloid hemangioma (GH) was first conceived in 1990 by Chan *et al.* to describe a rare and histologically distinctive benign vascular neoplasm occurring in patients affected by multicentric Castleman's disease<sup>41</sup>. Glomeruloid hemangioma has also been associated with POEMS syndrome, representing the association of polyneuropathy, organomegaly,



**Figure 7A.** Glomeruloid hemangioma. The dermis features a proliferation of dilated vascular spaces containing a capillaries proliferation.



**Figure 7B.** Glomeruloid hemangioma. Small intravascular capillary proliferations mimic renal glomeruli.

endocrinopathy, M-protein, and skin changes). Importantly, authors identified this cutaneous vascular lesion as a hallmark of the syndrome.

Glomeruloid hemangioma presents either as a single lesion in non-syndromic patients or as multiple lesions in patients affected by Castleman's disease, POEMS syndrome or the even rarer TAFRO syndrome, in which the association of thrombocytopenia, anasarca, fever, renal failure and organomegaly is observed. In consideration of the heterogeneity of cutaneous manifestations among patients affected by POEMS syndrome, the incidence of GH is difficult to estimate.

However, it has been reported to vary between 26% to 44%. The highest prevalence is found among Asian patients. Importantly, very rarely cases of multiple glomeruloid hemangioma may also occur also in patients without POEMS syndrome.

Clinically, GH presents as eruptive red to violaceous papules, affecting the trunk and proximal limbs. Size ranges from few millimeters in diameter to few centimeters.

Microscopically, GH is composed of numerous dilated sinusoidal vascular channels located within the dermis and associated with small intravascular capillary proliferations arranged in a grape-like pattern mimicking renal glomeruli. (Figs. 7A, 7B). The vascular channels of the sinusoids are lined by flat endothelium while the capillary networks are lined by plump endothelial cells that may feature cytoplasmic vacuoles. A pericytic component is invariably present. Both endothelial and stromal elements may occasionally contain characteristic PASD-positive eosinophilic globules.

The authors have suggested a dual immunohistochemical profile differentiating the sinusoidal from the capillary component. Specifically, the former will show positivity for CD31 and CD68 and negative staining for CD34. On the other hand, capillary endothelial cells are CD31 and CD34 positive but CD68 negative. Glomeruloid hemangioma seems to be distinct from the recently reported entity named papillary hemangioma that also features the presence of eosinophilic globules<sup>42</sup>.

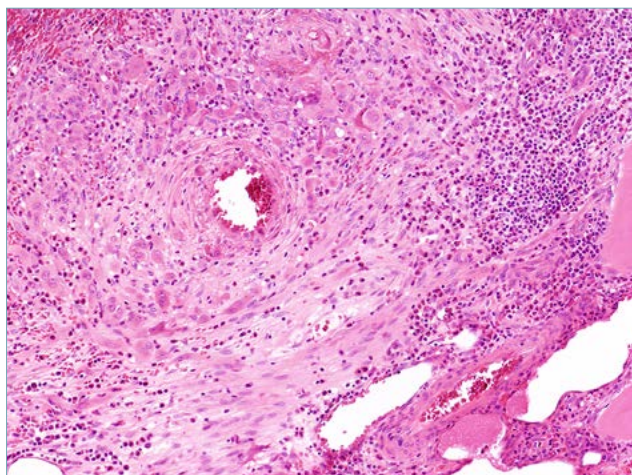
Glomeruloid hemangioma is a benign lesion hence no specific treatment is needed. Nonetheless, GH should raise a red flag for clinicians to investigate a possible association with POEMS syndrome.

#### EPITHELIOD HEMANGIOMA

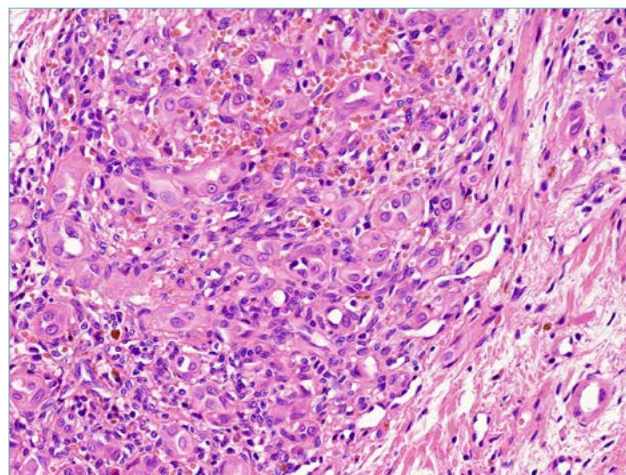
Epithelioid hemangioma was first reported in soft tissues in the 1969 as angiolymphoid hyperplasia with eosinophilia (ALHE)<sup>43</sup>. Later Juan Rosai introduced for the first time the descriptive label "histiocytoid hemangioma" (HH) that included also ALHE<sup>44-46</sup>. Subsequently, this term was abandoned, because in the original description this definition encompassed several entities therefore generating potential diagnostic confusion. To date, according to current WHO classification, the term epithelioid hemangioma (EH), introduced in the late 80s by Weiss and Rosai<sup>47</sup>, is to be preferred.

Epithelioid hemangioma is a benign vascular neoplasm affecting patients with a wide age range (from 23 to 75 years; median age 45 years) that presents as single, slow-growing erythematous to red-brown angiomatous papules or nodules in the dermis. Up to 20% of cases may exhibit multiple nodules, within the same anatomic region. Most cases occur in the skin

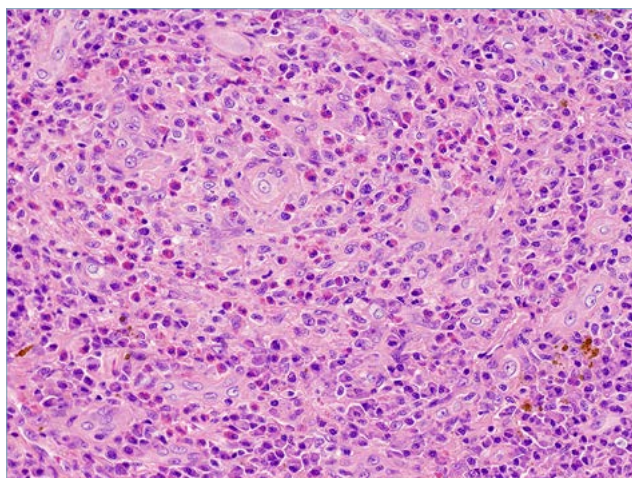




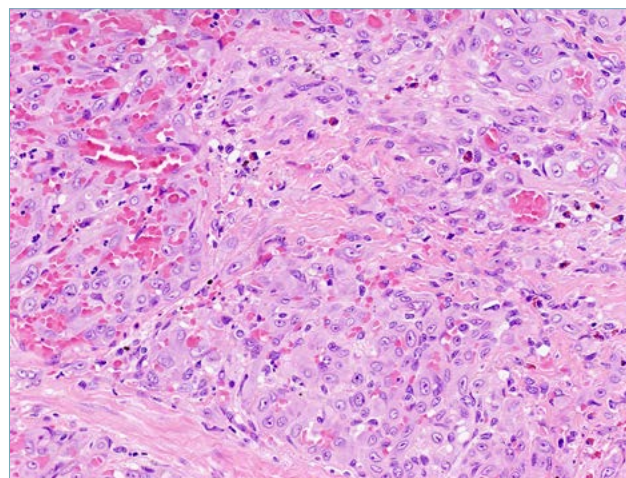
**Figure 8A.** Epithelioid hemangioma. Vascular channels are associated with prominent eosinophilic inflammatory infiltrate.



**Figure 8C.** Epithelioid hemangioma. The presence of intracytoplasmic lumina represents a frequent feature.



**Figure 8B.** Epithelioid hemangioma. Endothelial cells feature a distinctive epithelioid morphology.



**Figure 8D.** Epithelioid hemangioma. Solid endothelial growth is seen in cellular/atypical EH.

of the head and neck, especially in the pre-auricular area, forehead and scalp. Less usual sites include distal extremities, oral cavity, trunk, genital skin, lymph nodes and bone <sup>48</sup>. Visceral site and large vessels could be rarely involved. Localized tenderness, itching and occasional bleeding are the most common patient complaints. Some patients may present with mild systemic eosinophilia.

At low magnification, EH appears as well-circumscribed nodules. At higher magnification a proliferation of vascular channels associated with an abundant eosinophil-rich inflammatory component is observed (Fig. 8A) Epithelioid hemangioma is characterized by

a highly distinctive type of epithelioid endothelial lining. The vague resemblance to histiocytes justifies the old terminology (histiocytoid hemangioma) introduced by Rosai. The endothelial elements are in fact large and epithelioid with abundant eosinophilic cytoplasm and round to oval vesicular nuclei (Fig. 8B). Intravascular proliferations may be present, and atypia is generally mild. Endothelial cells exhibit variably sized intracytoplasmic vacuoles representing intracytoplasmic lumina (Fig. 8C). Rarely, clustering of endothelial cells with formation of solid areas, often associated with mild cytologic atypia has been reported as cellular/atypical EH (Fig. 8D) <sup>49</sup>. Immunohistochemically,

the epithelioid endothelial elements are strongly reactive for CD31 and ERG. Interestingly, FOS and FOSB gene rearrangements represent a relatively frequent occurrence (found in up to a third of cases) leading to FOS/FOSB nuclear overexpression<sup>50</sup>. However, it is our experience that cases of epithelioid hemangioma are often FOSB positive without FOSB gene rearrangements.

Focal expression of pan-cytokeratin is relatively often observed and, if associated with solid areas, may represent a potential diagnostic pitfall. Pericytic lining is most often preserved, and highlighted by positive smooth muscle actin staining.

Clinical data and specific histologic features distinguish EH from Kimura disease, with which EH was often confused in the past. Kimura disease however does show prominent eosinophilia, but lacks epithelioid endothelium. Epithelioid hemangioma may be confused with epithelioid hemangioendothelioma (EHE). However, EHE is characterized by *CAMTA1* or *TFE3* gene fusions gene, that led to nuclear expression of proteins thereof<sup>51</sup>.

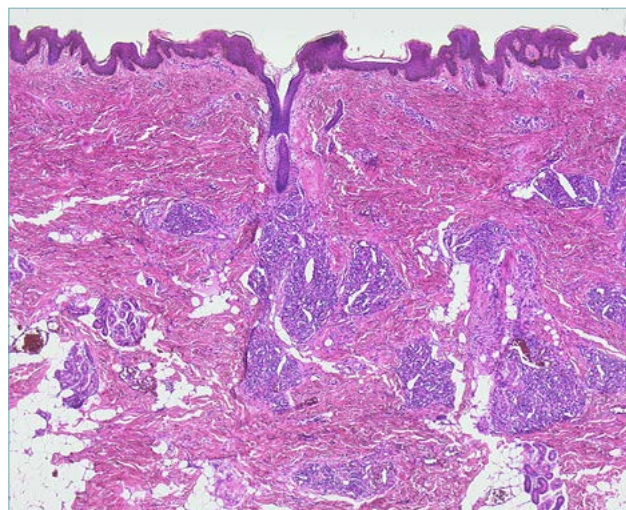
Epithelioid hemangioma is characterized by an indolent behavior. One-third of patients show local recurrence, although to date there are no reports of distant metastases.

#### TUFTED ANGIOMA

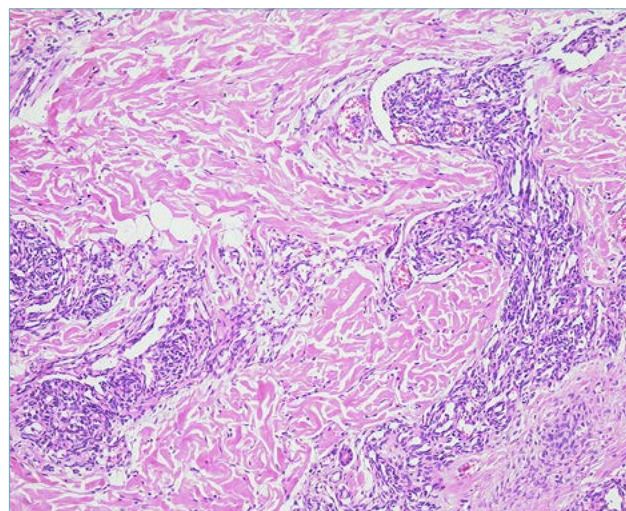
The reappraisal of tufted angioma (TA) is another important Rosai's contribution to the better understanding of vascular tumors<sup>52</sup>. First reported in the Japanese literature in 1949<sup>53</sup> Rosai suggested that TA is part of the spectrum of capillary hemangiomas.

Clinically, TA is an acquired bluish to erythematous nodule, plaque or macule that tends to progress slowly over time<sup>54</sup>. Spontaneous regression has been reported only exceptionally. Tufted angioma most commonly affect children and young adults without gender predilection, and are most frequently found in the neck, upper trunk, back and scalp. Multiple, congenital or familial autosomal dominant cases are uncommon, but have been described.

Tufted angioma have an exceptionally characteristic histologic appearance. On microscopy, the lesions are composed of numerous irregularly distributed and highly cellular capillary lobules (so called "cannon balls") (Fig. 9A) located within the dermis and sometimes the subcutis. The vascular proliferations consist of a central prominent vessel with distinct endothelial lining surrounded concentrically by smaller caliber capillaries with plump to flattened endothelium. Pericytes may also be visibly prominent within the lesion. Each vascular nodule is separated by normal dermal tissue, and at times the lobules may push



**Figure 9A.** Tufted angioma. At low power magnification so called "cannon balls" represent the morphologic hallmark of TA.



**Figure 9B.** Tufted angioma. Crescent-like vascular spaces are typically seen at the periphery of the proliferating nodules.

an outer vessel to form a crescent shaped vascular space (Fig. 9B). Mitoses are rare and cellular atypia is not present. Rarely, patients can present with multiple lesions displaying platelet trapping and Kasabach-Merritt syndrome may occur.

Main differential diagnoses are with nodular Kaposi sarcoma, from which it may be differentiated by its clinical presentation, and absence of HHV8 expression. Some authors have suggested that TA could rep-

represent a superficial, self-limiting variant of Kaposiform hemangioendothelioma<sup>55</sup>.

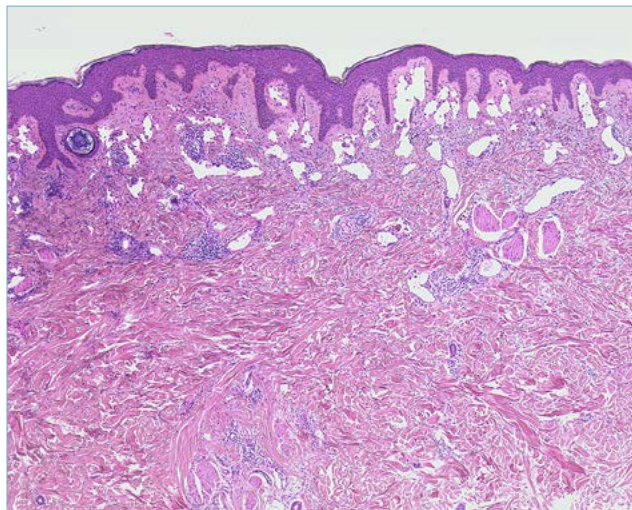
Complete surgical excision is the treatment of choice for smaller lesions, but often not feasible for larger lesions. Local recurrences tend to be rather common.

#### HOBNAIL HEMANGIOMA

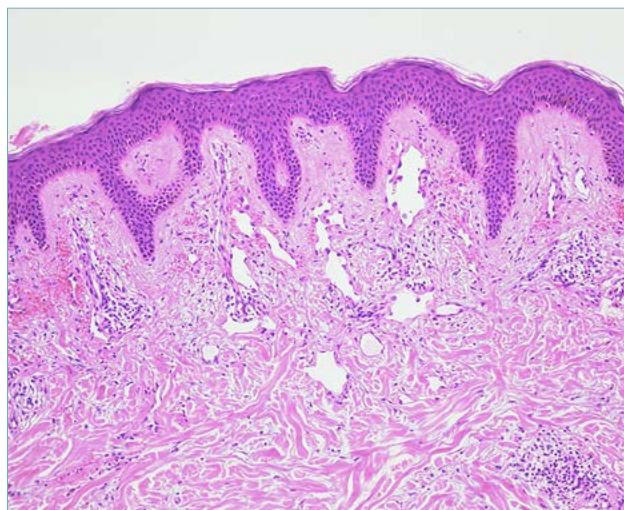
The relationships between hobnail hemangioma and targetoid hemosiderotic hemangioma still represent an unsettled debate. Targetoid hemosiderotic hemangioma is a vascular lesion with a distinctive clinical “target-like” appearance that was first described by Santa Cruz and Aronberg in 1988<sup>56</sup>. In 1999, Guillou et al. reported a series of 15 cutaneous vascular lesions clinically not always appearing as targetoid lesions, but all sharing a plump “hobnail” endothelial lining. Such feature awarded the lesion the more microscopically descriptive label “hobnail hemangioma” (HH)<sup>57</sup>.

Hobnail hemangioma is predominantly a single subcutaneous lesion, commonly arising in the limbs and trunk of young or middle-age patients. The face is rarely affected, although cases involving the tongue and mucosa have been reported.

Microscopically HH is composed of a well-formed vascular channel, irregularly dissecting the dermis (Fig. 10A). The vessels at the center of the lesion are lined by hobnail endothelial cells (Fig. 10B) with scant cytoplasm and may be associated with fibrin thrombi. Some of the dilated capillaries display intraluminal papillary projections without prominent endothelial atypia, multilayering or tufting. Mitoses are uncommon. The outer and deeper portion of the lesion are often compressed and lined by a flat endothelium.



**Figure 10A.** Hobnail hemangioma. Dilated vascular spaces appears to dissect the upper dermis.



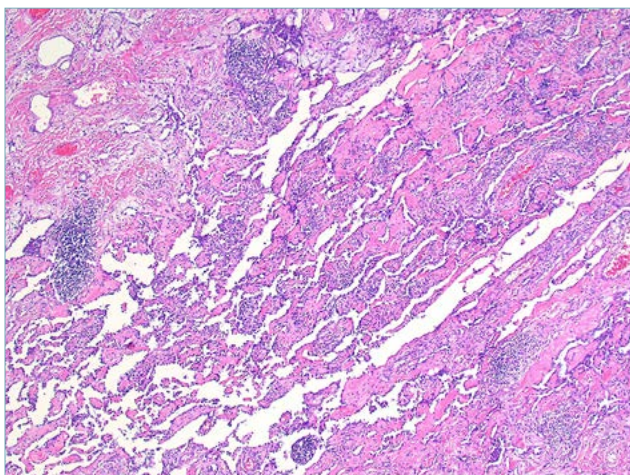
**Figure 10B.** Hobnail hemangioma. The typical hobnail appearance of endothelial cells is the diagnostic hallmark of the lesion.

A variable amount of perivascular lymphohistiocytic inflammatory infiltrate and minimal to abundant erythrocyte extravasation with subsequent hemosiderin deposition is observed. Endothelial cells in hobnail hemangioma stain positively for podoplanin, but show loss of expression of WT-1. Given this, it has been suggested that these lesions should be (again) renamed as superficial lymphatic vascular malformation<sup>58</sup>.

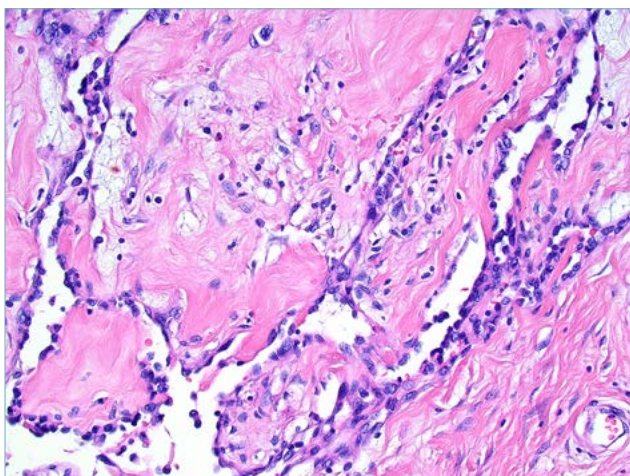
The differential diagnosis is mostly with patch stages of Kaposi's sarcoma that typically exhibits a peri-adnexal growth pattern, is associated with a lymphoplasmacytic infiltrate and consistently express HHSV8. Hobnail hemangioma is benign with no risk on local recurrence or metastatic spread<sup>59</sup>.

#### RETIFORM HEMANGIOENDOTHELIOMA

In 1994, Calonje et al. first described a novel, exceedingly rare, vascular entity that based on resemblance with rete testis was named retiform hemangioendothelioma (RH)<sup>60</sup>. The newly described lesion is currently classified as an intermediate grade vascular tumor which, to date, shows no tumor-related deaths. Clinically, RH presents a cutaneous, slow growing erythematous to violaceous plaque, often composed of confluent nodules. Most lesions arise in patients in the second to fourth decade of life (from 9 to 78 years old, mean age 36 years old), without sex predilection. The distal upper and lower limbs, followed by the trunk, penis and scalp are the more commonly involved anatomic sites. In two patients, development of multiple lesions at different anatomic sites has been reported.



**Figure 11A.** Retiform hemangioendothelioma. The arborizing pattern of growth of blood vessels somewhat mimic rete testis.



**Figure 11B.** Retiform hemangioendothelioma. Vascular spaces are lined by monomorphic hobnail endothelium.

Morphologically, RH exhibits a diffuse proliferation of ectatic arborizing vascular channels arranged in a retiform pattern that dissects the dermis and the subcutis (Fig. 11A). The newly formed vessels are lined by a monomorphic hobnail endothelium featuring minimal cytologic atypia (Fig. 11B). Few mitotic figures and focal intravascular proliferations without true papillary formation may be observed. Focal areas featuring spindle or epithelioid endothelium may be present. An accompanying lymphocytic infiltration is seen in most cases, which may vary from moderate to very prominent, almost obscuring the vasoformative lesion.

Immunohistochemically, the endothelial lining of RH shows invariable positivity for factor VIII, CD31, CD34 and ERG and negative staining for cytokeratin. Conflicting studies have shown variable D2-40 immunohistochemical results.

Papillary intralymphatic angioendothelioma (formerly known as Dabska's tumor) is a form of pediatric intermediate vascular neoplasm, which has been associated with RH. Even if PILA may share with RH variable endothelial hobnailing, distinction is facilitated by the absence of a prominent retiform pattern of growth, and by the presence of striking intravascular papillary formation featuring hyaline collagenous cores.

Retiform hemangioendothelioma is regarded by current WHO classification as an intermediate grade soft tissue tumor that shows local recurrence (2/3 of patients) and that may rarely metastasize to regional lymph nodes. Distant metastases or disease-related deaths have not been reported.

## Conclusions

Accurate morphologic classification of tumors represents a key step for proper treatment. Juan Rosai is part of a generation of pathologists that have brought surgical pathology at the center of the process of clinical decision. Importantly, even if in the last three decades immunohistochemistry, and more recently molecular genetics have been gradually implemented in the diagnostic process, Rosai's contributions demonstrate that H&E morphology fully retains its value. This represents a fundamental lesson not only for those who had the chance to be inspired directly by him, but also for pathologists in training. Whatever the sophistication of available techniques, pathology remains a "clinical" discipline, in which laboratory results need to be integrated by an expert eye strictly in context with morphology. This is certainly true for most fields of oncologic pathology, and mesenchymal tumors make no exception.

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## Authors' contributions

All authors contributed to the writing and the editing of the manuscript.

## Ethical consideration

No ethical issue was raised by this work.

## References

- 1 A WHO Classification of Tumours Editorial Board. Soft Tissue and Bone Tumours. Lyon (France): International Agency for Research on Cancer; 2020. (WHO Classification of Tumours Series, 5th ed.; vol. 3).
- 2 Sbaraglia M, Bellan E, Dei Tos AP. The 2020 WHO Classification of Soft Tissue Tumours: news and perspectives. *Pathologica* 2021;113:70-84. Epub 2020 Nov 3. <https://doi.org/10.32074/1591-951X-213>
- 3 Sbaraglia M, Dei Tos AP. The pathology of soft tissue sarcomas. *Radiol Med* 2019;124:266-281. Epub 2018 Jun 12. <https://doi.org/10.1007/s11547-018-0882-7>
- 4 Gerald WL, Miller HK, Battifora H, et al. Intra-abdominal desmoplastic small round-cell tumor. Report of 19 cases of a distinctive type of high-grade polyphenotypic malignancy affecting young individuals. *Am J Surg Pathol* 1991;15:499-513. PMID: 1709557.
- 5 Gerald WL, Rosai J. Case 2. Desmoplastic small cell tumor with divergent differentiation. *Pediatr Pathol* 1989;9:177-183. <https://doi.org/10.3109/15513818909022347>
- 6 Parkash V, Gerald WL, Parma A, et al. Desmoplastic small round cell tumor of the pleura. *Am J Surg Pathol* 1995;19:659-665. <https://doi.org/10.1097/0000478-199506000-00006>
- 7 Cummings OW, Ulbright TM, Young RH, et al. Desmoplastic small round cell tumors of the paratesticular region. A report of six cases. *Am J Surg Pathol* 1997;21:219-225. <https://doi.org/10.1097/0000478-199702000-00013>
- 8 Su MC, Jeng YM, Chu YC. Desmoplastic small round cell tumor of the kidney. *Am J Surg Pathol* 2004;28:1379-1383. <https://doi.org/10.1097/01.pas.0000128676.64288.0f>
- 9 Cai Z, Zhang L, Karni RJ, et al. Desmoplastic small round cell tumor of parotid gland: a rare entity with diagnostic challenge. *Int J Surg Pathol* 2020;28:782-786. Epub 2020 Apr 3. <https://doi.org/10.1177/1066896920913109>
- 10 Tison V, Cerasoli S, Morigi F, et al. Intracranial desmoplastic small-cell tumor. Report of a case. *Am J Surg Pathol* 1996;20:112-117. <https://doi.org/10.1097/0000478-199601000-00013>
- 11 Lae ME, Roche PC, Jin L, et al. Desmoplastic small round cell tumor: a clinicopathologic, immunohistochemical, and molecular study of 32 tumors. *Am J Surg Pathol* 2002;26:823-835. <https://doi.org/10.1097/0000478-200207000-00001>
- 12 Ladanyi M, Gerald W. Fusion of the EWS and WT1 genes in the desmoplastic small round cell tumor. *Cancer Res* 1994;54:2837-2840. PMID: 8187063.
- 13 Gerald WL, Rosai J, Ladanyi M. Characterization of the genomic breakpoint and chimeric transcripts in the EWS-WT1 gene fusion of desmoplastic small round cell tumor. *Proc Natl Acad Sci U S A* 1995;92:1028-1032. <https://doi.org/10.1073/pnas.92.4.1028>
- 14 Schoolmeester JK, Folpe AL, Nair AA, et al. EWSR1-WT1 gene fusions in neoplasms other than desmoplastic small round cell tumor: a report of three unusual tumors involving the female genital tract and review of the literature. *Mod Pathol* 2021;34:1912-1920. Epub 2021 Jun 7. <https://doi.org/10.1038/s41379-021-00843-5>
- 15 Sbaraglia M, Righi A, Gambarotti M, et al. Ewing sarcoma and Ewing-like tumors. *Virchows Arch* 2020;476:109-119. Epub 2019 Dec 4. <https://doi.org/10.1007/s00428-019-02720-8>
- 16 Wei G, Shu X, Zhou Y, et al. Intra-abdominal desmoplastic small round cell tumor: current treatment options and perspectives. *Front Oncol* 2021;11:705760. <https://doi.org/10.3389/fonc.2021.705760>
- 17 Stockman DL, Miettinen M, Suster S, et al. Malignant gastrointestinal neuroectodermal tumor: clinicopathologic, immunohistochemical, ultrastructural, and molecular analysis of 16 cases with a reappraisal of clear cell sarcoma-like tumors of the gastrointestinal tract. *Am J Surg Pathol* 2012;36:857-68. <https://doi.org/10.1097/PAS.0b013e31824644ac>
- 18 Zambrano E, Reyes-Mugica M, Franchi A, Rosai J. An osteoclast-rich tumor of the gastrointestinal tract with features resembling clear cell sarcoma of soft parts: reports of 6 cases of a GIST simulator. *Int J Surg Pathol* 2003;11:75-81. <https://doi.org/10.1177/106689690301100202>
- 19 Enzinger FM. Clear-cell sarcoma of tendons and aponeuroses. An Analysis of 21 Cases. *Cancer* 1965;18:1163-1174.
- 20 Chung EB, Enzinger FM. Malignant melanoma of soft parts. A reassessment of clear cell sarcoma. *Am J Surg Pathol* 1983;7:405-413.
- 21 Kraft S, Antonescu CR, Rosenberg AE, et al. Primary clear cell sarcoma of the tongue. *Arch Pathol Lab Med* 2013;137:1680-1683. <https://doi.org/10.5858/arpa.2012-0467-CR>
- 22 Feasel PC, Cheah AL, Fritchie K, et al. Primary clear cell sarcoma of the head and neck: a case series with review of the literature. *J Cutan Pathol* 2016;43:838-846. Epub 2016 Jul 15. <https://doi.org/10.1111/cup.12755>
- 23 Sbaraglia M, Zanatta L, Toffolatti L, et al. Clear cell sarcoma-like/malignant gastrointestinal neuroectodermal tumor of the tongue: a clinicopathologic and molecular case report. *Virchows Arch* 2021;478:1203-1207. Epub 2020 Oct 2. <https://doi.org/10.1007/s00428-020-02933-2>
- 24 Antonescu CR, Nafa K, Segal NH, et al. EWS-CREB1: a recurrent variant fusion in clear cell sarcoma--association with gastrointestinal location and absence of melanocytic differentiation. *Clin Cancer Res* 2006;12:5356-5362. <https://doi.org/10.1158/1078-0432.CCR-05-2811>
- 25 Goh GH, Teh M, Vanecek T, et al. Primary pulmonary clear cell sarcoma--the first two reported cases. *Virchows Arch* 2016;469:111-117. Epub 2016 Apr 25. <https://doi.org/10.1007/s00428-016-1943-8>
- 26 Pauwels P, Debiec-Rychter M, Sciort R, et al. Clear cell sarcoma of the stomach. *Histopathology* 2002;41:526-530. <https://doi.org/10.1046/j.1365-2559.2002.01509.x>
- 27 Wang WL, Mayordomo E, Zhang W, et al. Detection and characterization of EWSR1/ATF1 and EWSR1/CREB1 chimeric transcripts in clear cell sarcoma (melanoma of soft parts). *Mod Pathol* 2009;22:1201-1209. Epub 2009 Jun 26. <https://doi.org/10.1038/modpathol.2009.85>
- 28 Steeper TA, Rosai J. Aggressive angiomyxoma of the female pelvis and perineum. Report of nine cases of a distinctive type of gynecologic soft-tissue neoplasm. *Am J Surg Pathol* 1983;7:463-475. <https://doi.org/10.1097/0000478-198307000-00009>
- 29 Granter SR, Nucci MR, Fletcher CD. Aggressive angiomyxoma: reappraisal of its relationship to angioyofibroblastoma in a series of 16 cases. *Histopathology* 1997;30:3-10. <https://doi.org/10.1046/j.1365-2559.1997.d01-556.x>
- 30 Micci F, Panagopoulos I, Bjerkehagen B, et al. Dereglulation of HMGA2 in an aggressive angiomyxoma with t(11;12)(q23;q15). *Virchows Arch* 2006;448:838-842. Epub 2006 Mar 28. <https://doi.org/10.1007/s00428-006-0186-5>
- 31 McCluggage WG, Connolly L, McBride HA. HMGA2 is a sensitive but not specific immunohistochemical marker of vulvovagi-

- nal aggressive angiomyxoma. *Am J Surg Pathol* 2010;34:1037-1042. <https://doi.org/10.1097/PAS.0b013e3181e32a11>
- 32 Suster S, Rosai J. Intranodal hemorrhagic spindle-cell tumor with "amiantoid" fibers. Report of six cases of a distinctive mesenchymal neoplasm of the inguinal region that simulates Kaposi's sarcoma. *Am J Surg Pathol* 1989;13:347-357. PMID: 2712187.
- 33 Weiss SW, Gnepp DR, Bratthauer GL. Palisaded myofibroblastoma. A benign mesenchymal tumor of lymph node. *Am J Surg Pathol* 1989;13:341-346. PMID: 2712186.
- 34 Lee JY, Abell E, Shevechik GJ. Solitary spindle cell tumor with myoid differentiation of the lymph node. *Arch Pathol Lab Med* 1989;113:547-550. PMID: 2712680.
- 35 Fletcher CD, Stirling RW. Intranodal myofibroblastoma presenting in the submandibular region: evidence of a broader clinical and histological spectrum. *Histopathology* 1990;16:287-293. <https://doi.org/10.1111/j.1365-2559.1990.tb01117.x>
- 36 Laskin WB, Lasota JP, Fetsch JF, et al. Intranodal palisaded myofibroblastoma: another mesenchymal neoplasm with CTNFB1 ( -catenin gene) mutations: clinicopathologic, immunohistochemical, and molecular genetic study of 18 cases. *Am J Surg Pathol* 2015;39:197-205. <https://doi.org/10.1097/PAS.0000000000000299>
- 37 Suster S, Rosai J. Hamartoma of the scalp with ectopic meningotheelial elements. A distinctive benign soft tissue lesion that may simulate angiosarcoma. *Am J Surg Pathol* 1990;14:1-11. <https://doi.org/10.1097/00000478-199001000-00001>
- 38 Rosai J, Sumner HW, Kostianovsky M, et al. Angiosarcoma of the skin. A clinicopathologic and fine structural study. *Hum Pathol* 1976;7:83-109. [https://doi.org/10.1016/s0046-8177\(76\)80007-x](https://doi.org/10.1016/s0046-8177(76)80007-x)
- 39 Eusebi V, Carcangiu ML, Dina R, Rosai J. Keratin-positive epithelioid angiosarcoma of thyroid. A report of four cases. *Am J Surg Pathol* 1990;14:737-747. <https://doi.org/10.1097/00000478-199008000-00004>
- 40 Fletcher CD, Beham A, Bekir S, et al. Epithelioid angiosarcoma of deep soft tissue: a distinctive tumor readily mistaken for an epithelial neoplasm. *Am J Surg Pathol* 1991;15:915-924. <https://doi.org/10.1097/00000478-199110000-00001>
- 41 Chan JK, Fletcher CD, Hicklin GA, Rosai J. Glomeruloid hemangioma. A distinctive cutaneous lesion of multicentric Castlemann's disease associated with POEMS syndrome. *Am J Surg Pathol* 1990;14:1036-1046. <https://doi.org/10.1097/00000478-199011000-00005>
- 42 Suurmeijer AJ, Fletcher CD. Papillary haemangioma. A distinctive cutaneous haemangioma of the head and neck area containing eosinophilic hyaline globules. *Histopathology* 2007;51:638-648. <https://doi.org/10.1111/j.1365-2559.2007.02847.x>
- 43 Wells GC, Whimster IW. Subcutaneous angiolymphoid hyperplasia with eosinophilia. *Br J Dermatol* 1969;81:1-14. <https://doi.org/10.1111/j.1365-2133.1969.tb15914.x>
- 44 Rosai J, Gold J, Landy R. The histiocytoid hemangiomas. A unifying concept embracing several previously described entities of skin, soft tissue, large vessels, bone, and heart. *Hum Pathol* 1979;10:707-730. [https://doi.org/10.1016/s0046-8177\(79\)80114-8](https://doi.org/10.1016/s0046-8177(79)80114-8). PMID: 527967.
- 45 Rosai J. Histiocytoid hemangioma. A proposal of a new entity which embraces previously described diseases of heart, blood vessels, skin, bone and other sites. *J Fla Med Assoc* 1980;67:190-191. PMID: 7359110.
- 46 Rosai J. Angiolymphoid hyperplasia with eosinophilia of the skin. Its nosological position in the spectrum of histiocytoid hemangioma. *Am J Dermatopathol* 1982;4:175-184. <https://doi.org/10.1097/00000372-198204000-00013>
- 47 Luthringer DJ, Virmani R, Weiss SW, Rosai J. A distinctive cardiovascular lesion resembling histiocytoid (epithelioid) hemangioma. Evidence suggesting mesothelial participation. *Am J Surg Pathol* 1990;14:993-1000. <https://doi.org/10.1097/00000478-199011000-00001>
- 48 Righi A, Sbaraglia M, Gambarotti M, et al. Primary vascular tumors of bone: a monoinstitutional morphologic and molecular analysis of 427 cases with emphasis on epithelioid variants. *Am J Surg Pathol* 2020;44:1192-1203. <https://doi.org/10.1097/PAS.0000000000001487>. PMID: 32271190
- 49 Antonescu CR, Chen HW, Zhang L, et al. ZFP36-FOSB fusion defines a subset of epithelioid hemangioma with atypical features. *Genes Chromosomes Cancer* 2014;53:951-959. Epub 2014 Jul 18. <https://doi.org/10.1002/gcc.22206>
- 50 Huang SC, Zhang L, Sung YS, et al. Frequent FOS gene rearrangements in epithelioid hemangioma: a molecular study of 58 cases With Morphologic Reappraisal *Am J Surg Pathol* 2015;39:1313-1321. <https://doi.org/10.1097/PAS.0000000000000469>
- 51 Doyle LA, Fletcher CD, Hornick JL. Nuclear expression of CAMTA1 distinguishes epithelioid hemangioendothelioma from histologic mimics. *Am J Surg Pathol* 2016;40:94-102. <https://doi.org/10.1097/PAS.0000000000000511>
- 52 Padilla RS, Orkin M, Rosai J. Acquired "tufted" angioma (progressive capillary hemangioma). A distinctive clinicopathologic entity related to lobular capillary hemangioma. *Am J Dermatopathol* 1987;9:292-300. <https://doi.org/10.1097/00000372-198708000-00002>
- 53 Cho KH, Kim SH, Park KC, et al. Angioblastoma (Nakagawa)--is it the same as tufted angioma? *Clin Exp Dermatol* 1991;16:110-113. <https://doi.org/10.1111/j.1365-2230.1991.tb00318.x>
- 54 Mentzel T, Wollina U, Castelli E, et al. Büschelartiges Hämangiom ("tufted angioma"). Klinisch-pathologische und immunhistologische Analyse von fünf Fällen einer distinkten Entität im Spektrum der kapillären Hämangiome [Tufted hemangioma. Clinicopathologic and immunohistologic analysis of 5 cases of a distinct entity within the spectrum of capillary hemangioma]. *Hautarzt* 1996;47:369-375. German. <https://doi.org/10.1007/s001050050433>
- 55 Chu CY, Hsiao CH, Chiu HC. Transformation between Kaposiform hemangioendothelioma and tufted angioma. *Dermatology* 2003;206:334-337. <https://doi.org/10.1159/000069947>
- 56 Santa Cruz DJ, Aronberg J. Targetoid hemosiderotic hemangioma. *J Am Acad Dermatol* 1988;19:550-558. [https://doi.org/10.1016/s0190-9622\(88\)70211-x](https://doi.org/10.1016/s0190-9622(88)70211-x)
- 57 Guillou L, Calonje E, Speight P, et al. Hobnail hemangioma: a pseudomalignant vascular lesion with a reappraisal of targetoid hemosiderotic hemangioma. *Am J Surg Pathol* 1999;23:97-105. <https://doi.org/10.1097/00000478-199901000-00011>
- 58 Trindade F, Kutzner H, Tellechea Ó, et al. Hobnail hemangioma reclassified as superficial lymphatic malformation: a study of 52 cases. *J Am Acad Dermatol* 2012;66:112-115. Epub 2011 Aug 6. <https://doi.org/10.1016/j.jaad.2011.05.019>
- 59 Mentzel T, Partanen TA, Kutzner H. Hobnail hemangioma ("targetoid hemosiderotic hemangioma"): clinicopathologic and immunohistochemical analysis of 62 cases. *J Cutan Pathol* 1999;26:279-286. <https://doi.org/10.1111/j.1600-0560.1999.tb01845.x>
- 60 Calonje E, Fletcher CD, Wilson-Jones E, Rosai J. Retiform hemangioendothelioma. A distinctive form of low-grade angiosarcoma delineated in a series of 15 cases. *Am J Surg Pathol* 1994;18:115-25. PMID: 8291650.